High Production Volume Chemical Challenge Program

- Final -
Test Plan for
Dicamba Intermediates Category

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1.0 Introduction

1.1 Overview

BASF Corporation (BC) hereby submits the final version of the robust summaries and completed test plan for the Dicamba Intermediates Category of chemicals, under the United States Environmental Protection Agency's (U.S. EPA) High Production Volume (HPV) Chemical Challenge Program. This document addresses seven HPV sponsored chemicals[1], all of which are intermediates found in the production of dicamba (see Table 1). Data from one non-HPV chemical is used to support the chemical category via read across. Data read across occurs when physicochemical and toxicological data from one chemical are used for another chemical, and is done only when the two chemicals are deemed sufficiently similar in structure that they are likely to have similar chemical and toxicological properties.

The purpose of this plan was to develop screening level data on the physicochemical properties, environmental fate, ecotoxicity, and mammalian toxicity of seven HPV chemicals consistent with the Screening Information Data Set (SIDS). The original (2001) plan summarized the existing SIDS data for the seven HPV sponsored chemicals and made recommendations for testing to fill any data gaps in the SIDS endpoints. As the U.S. EPA has encouraged the use of chemical categories where scientifically justified to reduce animal testing, a category approach was developed for this plan.

Hefter et. al. (1999) defined a chemical category for the purposes of the HPV program to be a group of substances whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern, as a result of structural similarity. A Dicamba Intermediates category was developed for these chemicals based on structural similarities and uses data read across where scientifically justified to fill data gaps in the SIDS endpoints.

Table 1
Summary of chemicals in the Dicamba Intermediates Category.

CAS Number	Name	Remark
1982-69-0	Dicamba, sodium salt (3,6-Dichloro-2-methoxybenzoic acid, sodium salt)	HPV
68938-79-4	3,6-Dichloro-2-hydroxybenzoic acid, potassium sodium salt	HPV
68938-80-7	3,6-Dichloro-2-hydroxybenzoic acid, dipotassium salt	HPV
583-78-8	2,5-Dichlorophenol	HPV
52166-72-0	2,5-Dichlorophenol, sodium salt	HPV
68938-81-8	2,5-Dichlorophenol, potassium salt	HPV
1984-58-3	2,5-Dichloroanisole	HPV
1918-00-9	Dicamba (3,6-dichloro-2-methoxybenzoic acid)	Supporting

HPV = Chemical sponsored by BASF Corporation under the U.S. EPA HPV program.
Supporting = Chemical that is physicochemically and/or toxicologically similar, and is used to support the chemical category.

[1] The original test plan included two chemical intermediates used in the production of acifluorfen. As indicated in a letter to U.S. EPA dated Jan 23, 2004, BC sold all interest in this product line to United Phosphorus Limited in 2003 and as a consequence withdrew further sponsorship of these chemicals under the HPV Challenge Program

1.2 Use and Exposure Information

The chemicals in this category are all considered closed system intermediates used in the manufacture of the herbicide dicamba. BASF dicamba production occurs at one site, in Beaumont, Texas. Production volumes of each of the dicamba intermediates at the Beaumont facility are from 5 – 15 million pounds per year. These chemicals exist in process streams diluted by various aqueous and organic solutions. Processing occurs in closed systems with no routine exposure possible except for sampling. While approximately 25 – 50 workers are potentially exposed at the Beaumont facility, all sampling is performed with the proper personal protective equipment (PPE) using sample stations designed to minimize the possibility of exposure. All samples are handled in lab settings according to a chemical hygiene plan and using engineering controls such as fume hoods.

Industrial hygiene monitoring conducted at the facility during the period 1998 – 2005 has demonstrated that exposure levels are well below Occupational Exposure Limit (OEL) values set by OSHA, ACGIH or other organizations. For dicamba, sodium salt, the maximum measured exposure was 38% of the ACGIH OEL of 10 mg/m^3 and 25% of the OSHA OEL of 15 mg/m^3. For dichlorophenol, the maximum measured exposure was 1% of the AIHA OEL of 1 ppm. Monitoring data are not available for the other chemicals; however, all of the intermediates are either rather non-volatile liquids or salts so the probability of exposure by inhalation is quite low. Dermal exposures are prevented through worker training, the use of proper PPE, and engineering controls.

The vast majority of the intermediates formed are converted to the desired product and thus the inventory on site at any one time is small. The primary waste streams are aqueous streams that are treated on site. Organic waste streams are small and are incinerated. Potential environmental exposures are limited to spills on site, which are handled in accordance with site safety procedures. In summary, the closed system intermediates of dicamba manufactured at the Beaumont site pose a minimal exposure threat to workers and the environment.

1.3 Methods for Data Review of SIDS Endpoints

A review of the scientific literature and BASF Corporation's company data was conducted on the physicochemical properties, environmental fate and effects, and mammalian toxicity endpoints for the eight chemicals in the Dicamba Intermediates category. Searches were conducted using CAS numbers and chemical names in the following databases: TOXLINE, ECOTOX, MEDLINE, and CHEMID. Standard handbooks and databases (*e.g.* CRC Handbook on Chemicals, IUCLID, Merck Index, etc.) were consulted for physicochemical properties. Numerous individual studies, reports and other data sources were reviewed in development of this test plan. The literature was updated in January 2007 and October 2007 to determine if any newly published studies would add to or impact the data package.

In accordance with U.S. EPA guidance, in those instances where measured physicochemical parameters and environmental fate data were not available, these properties were developed using EPIWIN (version

3.20) modeling. EPIWIN is an acronym for the Estimation Programs Interface for Microsoft Windows 3.1 (June 1998), and is a package of computer programs developed by the U.S. EPA Office of Pollution Prevention and Toxics that uses computational methods and structure-activity relationships (SAR) in estimating chemical properties, environmental fate and aquatic toxicity of organic chemicals. Due to the inherent limitations of SAR approaches, EPIWIN modeling may produce non-realistic estimates; therefore, EPIWIN data are evaluated for reasonableness prior to use. In accordance with U.S. EPA guidance, environmental fate and transport estimates were developed using the level III equilibrium criteria model (EQC) in EPIWIN v3.20 as described in Mackay et al. (1996).

Robust summaries were prepared for studies to provide a detailed summary of the test methods and results. Though several studies may have been evaluated for a particular SIDS endpoint, robust summaries were prepared only for the critical study that represented the best available data. Selection of the critical study was based on a review of all studies using the ranking system developed by Klimisch et al (1997), as well as the criteria outlined in the U.S. EPA's methods for determining the adequacy of existing data.

Based on the robust summaries, reasonable read across methodologies and scientific expertise, a testing plan was developed and submitted to the EPA for review. After comments by the EPA and others, the testing originally proposed by BC and the additional testing requested by EPA was conducted. The studies have now been completed, robust summaries of the new results have been prepared, and the data tables filled with the new results to address all data gaps in the SIDS recommended paradigm.

2.0 Dicamba Intermediates Category

2.1 Category Analysis

This plan addresses seven HPV chemicals under the Dicamba Intermediates Category, which is comprised of two groups (see Table 2). The substances under evaluation are all intermediates found in the production of dicamba, and include the salts and acids of dicamba. Specific discussions regarding the justification of the categories are presented in Section 3. The chemical categories were developed in accordance with the EPA's recommendation in that substances within each group have physicochemical and/or toxicological properties that are likely to be similar, and follow a regular pattern, as a result of structural similarities. The similarities are based on a common functional group, common precursors or breakdown products (that is, structurally similar chemicals), and an incremental and constant change across the category.

Table 2
Summary of Groups within the Dicamba Intermediates Category.

Group 1
Dicamba (3,6-dichloro-2-methoxybenzoic acid) [1918-00-9] [Supporting chemical]
Dicamba, sodium salt (3,6-Dichloro-2-methoxybenzoic acid, sodium salt) [1982-69-0]
3,6-Dichloro-2-hydroxybenzoic acid, potassium sodium salt [68938-79-4]
3,6-Dichloro-2-hydroxybenzoic acid, dipotassium salt [68938-80-7]
Group 2
2,5-Dichlorophenol [583-78-8]
2,5-Dichlorophenol, sodium salt [52166-72-0]
2,5-Dichlorophenol, potassium salt [68938-81-8]
2,5-Dichloroanisole [1984-58-3]

2.2 Salts and Acids

The substances under evaluation are all intermediates in the production of dicamba including salt and acid forms of the same chemical. The acid and salt forms of the same chemical have many similar physicochemical and toxicological properties; therefore, data read across is used for those instances where data are available for the acid form but not the salt, and vice versa. This position is based on experimental studies that have clearly demonstrated a high degree of similarity between the toxicokinetics and toxicodynamics of acid and salt forms of the same chemical. In fact, when reviewing the results of a metabolic study with dicamba in rats, the U.S. EPA Data Evaluation Record (DER) stated: “Results indicate that there were no significant differences in absorption, distribution, metabolism and excretion among dicamba free acid and its three amine salts.” Regarding physicochemical properties and fate, the “read across” method is valid where the original physical form of the material is irrelevant to the endpoint. This would include biodegradation at high dilutions, water stability at defined pH, and transport/distribution at high dilution. Read across does not apply for other parameters dependent upon bulk physicochemical properties, such as melting point, vapor pressure, boiling point, initial transport/distribution in the environment (conditions near the relevant discharge source), partition coefficient in unbuffered systems and water solubility. Logic and judgment must be used when making assessments about actual systems based on pKa values, pH levels and bulk chemical properties. Mackay et al (1996) states that for Type 5 compounds (substances that can exist as several reversibly interchangeable species, including carboxylic acids) additional work is needed in developing a more general model.

A general premise in regulatory toxicology is that test results with an acid form of a chemical are representative of test results with the same chemical as a salt. Many chemicals are marketed as various

salts to enhance water solubility, whereas toxicological testing is often done with the acid form. In the gastrointestinal tract, acids, bases and salts are absorbed in the undissociated (non-ionized) form by simple diffusion (Niesink,et al. 1996, , Klaassen, 1995, Hayes, 1994). In general the amount of dissociation of acids and bases is determined by the pKa (or pKb) values of the substance and the pH of the environment. The pH of the stomach varies between 1-3, and in the intestines pH values between 5 and 8 are reported (Niesink et al., 1996). In the aquatic environment, pH typically ranges between 6 and 9.

In an acidic environment, acids will be present mainly in the non-ionized form. The amount of dissociation depends on the strength of the acid (reflected by its pKa value) (Klaassen, 1995). Strong acids may be dissociated to some extent in very acidic environment like the stomach, but weaker acids will occur mainly undissociated. Salts may dissociate in an aqueous environment too, forming a cation and an anion. For the compounds under consideration in this document, the anion formed upon dissociation of the salt is the same as the anion resulting from dissociation of the acid. In the acidic environment of the stomach the generated anion (whether generated from the acid or the salt) will accept a proton and hence will be present as the free (undissociated) acid.

Both the acids and the salts will be present in (or converted to) the acid form in the stomach. This means that for both types of parent chemical (acid or salt) the same compounds eventually enter the small intestine, where the equilibrium, as a result of increased pH, will shift towards dissociation (ionized form) (Klaassen, 1995). Hence, the situation will be similar for compounds originating from salts and those originating from acids and therefore no differences in uptake are anticipated.

Metabolic studies for dicamba have been performed that demonstrate this position clearly (BASF,1994). For dicamba it was established that both the free acid and its salts showed similar dissociation patterns in water, under both basic and acidic conditions (BASF, 1993). Five amine salts (potassium, sodium, dimethylamine, isopropylamine and diglycolamine) were tested and each reached equilibrium of essentially 100% dissociation within 75 seconds in water with a reaction half life of less than 10 seconds. It was concluded that dicamba salts readily and quickly dissociate to the dicamba anion in aqueous solutions. An *in vivo* study in male rats with radiolabelled salts of dicamba did not show any differences between the salts and the free acid on absorption, distribution, metabolism and excretion (BASF, 1994). The U.S. EPA DER for this study stated: “Results indicate that there were no significant differences in absorption, distribution, metabolism and excretion among dicamba free acid and its three amine salts. Therefore, these results confirm the Registrant’s hypothesis that dicamba, as a free acid or as amine salt form will be rapidly dissociated and absorbed in the animal’s digestive system.”

This position is further supported by comparative toxicology results from studies conducted with the acid and the salts of dicamba, as presented in the DER. Rat oral LD_{50} values are very similar between the acid and five salts varying between 1352 and 1870 mg/kg-bw. Other acute tests demonstrated similar

dermal and inhalation toxicity as well as eye and skin irritation and skin sensitization. Genotoxicity tests conducted with the acid and three amine salts all demonstrated negative results for *in vitro* mutagenicity and *in vitro* and *in vivo* chromosomal aberration. Regarding environmental fate, U.S. EPA bridged the data requirements for the dicamba sodium and potassium salts and three amine salts on the basis of the rapid conversion of the dicamba salts to the free acid of dicamba (U.S. EPA, 2006).

For the other compounds there are no specific comparison studies of salts and acid; however, based on structural considerations (that is, absence of a carboxylic acid group or the positioning of electron withdrawing substituents farther away from the carboxylic acid group) 2,5-dichlorophenol is expected to be a weaker acid than dicamba. For weaker acids, it is expected that the relative amount of non-ionized acid present in the stomach will be even higher and that the situation after administration of the salt will resemble the situation after administration of the acid even more so than with dicamba. The environmental fate of the 2,5-dichlorophenol salts will be similar to that of the dicamba salts.

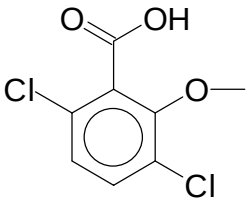
Based on these considerations it is concluded that uptake will not differ for acids and salts in the different categories, and the toxicology is expected to be the same. The environmental fate and effects are also expected to be similar for the acids and the salts Therefore, data read across is used for those instances where data is available for the acid form but not the salt, and vice versa.

3.0 Categorization

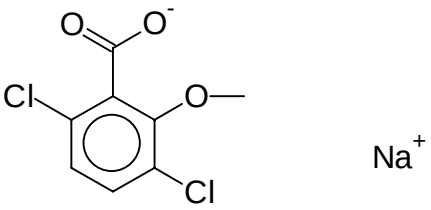
3.1 Group I

3.1.1 Chemistry

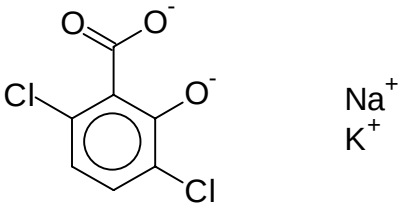
1. CAS 1918-00-9: Dicamba (3,6-dichloro-2-methoxybenzoic acid) – Supporting chemical



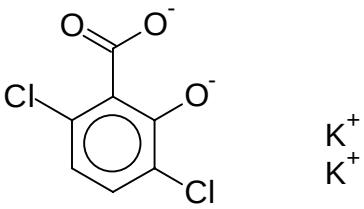
2. CAS 1982-69-0: Dicamba, sodium salt (3,6-Dichloro-2-methoxybenzoic acid, sodium salt)



3. CAS 68938-79-4: 3,6-Dichloro-2-hydroxybenzoic acid, potassium sodium salt



4. CAS 68938-80-7: 3,6-Dichloro-2-hydroxybenzoic acid, dipotassium salt



The HPV chemicals in Group I include the sodium salt of dicamba and two salt forms of the dicamba intermediate, 3,6-dichloro-2-hydroxybenzoic acid. Dicamba is included as a supporting chemical. All

chemicals in this group have a common, central structure consisting of a phenyl moiety with two chlorine atoms in para- position to each other. No difference in chemical behavior is therefore expected based on this part of the structure. Furthermore, all chemicals in Group I bear an oxygen atom that is directly attached to the phenyl ring. This oxygen atom is present either as part of a methoxyl group (chemicals 1 and 2) or a functionalized hydroxyl group (chemicals 3 and 4). Also, Group I chemicals contain a carboxylate moiety on the phenyl ring that is present as free carboxylic acid (chemical 1) or as sodium or potassium carboxylate (chemicals 2, 3, 4). The basis for the grouping of dicamba and its intermediate chemicals in Group I is the presence of this carboxylate moiety.

The carboxylate group is an electron withdrawing substituent and a mildly deactivating group (that is, deactivating the phenyl ring towards electrophilic aromatic substitution). In addition, halobenzenes that have such an electron withdrawing substituent in the ortho- or para- position relative to the halogen atom can undergo nucleophilic aromatic substitution. The appearance of the carboxylate group, in both the free carboxylic acid or carboxylate salt, does not influence these characteristics.

The different appearance of the oxygen atom as a methoxyl or hydroxyl group attached to the phenyl ring is not predicted to have a significant influence on the reactivity of the chemical. Both hydroxyl and methoxyl substituents are strongly activating ortho- and para-directors (that is, activating the phenyl ring towards electrophilic aromatic substitution). They activate the phenyl ring by resonance donation of oxygen pi electrons , and for this it does not matter whether the oxygen is present as a free or functionalized hydroxyl group or as part of the methoxyl group. Chemicals in Group I are, thus, expected to have equivalent chemical reactivity regardless of whether they contain a methoxyl or hydroxyl moiety.

3.1.2 Toxicokinetics and Toxicodynamics

The chemicals in Group I are 3,6-dichloro benzoic acid and three mono- or di-salts of 3,6-dichloro benzoic acid. Based on toxicokinetic studies both the salt forms and the acid form were found to have equivalent absorption from the gastrointestinal tract and other toxicokinetic processes, such as tissue distribution and systemic clearance (Caux et al., 1993; BASF, 1994). Again, the U.S. EPA DER for this study stated: “Results indicate that there were no significant differences in absorption, distribution, metabolism and excretion among dicamba free acid and its three amine salts.” In other related studies, dicamba is reported to be readily absorbed and excreted. In dairy cows 90% was excreted within 6 hours as the parent compound (72%) and an unidentified metabolite (18%) (Caux et al., 1993; Costa, 1997).

All the chemicals in Group I are expected to have similar biotransformation pathways and elimination rates due to the presence of the carboxyl group, which is expected to be the primary site for conjugation. In a study by Caux et al. (1993) the half-life of dicamba was reported to be 0.4 hours after dermal administration to rats. Demethylation is known to be a route of bacterial degradation of dicamba and cytochrome P450 oxidations in mammals are anticipated to lead to demethylation as well. In either case,

dicamba and its salt are converted partially to 3,6-dichlorosalicylic acid. The elimination of chemicals with the methoxyl group may be slower than those containing a hydroxyl group, but no significant difference in overall toxicity is expected. Furthermore, the sodium and/or potassium cation should not affect toxicity, since the sodium and potassium cations will be added to the large pools present in the body.

3.1.3 Group I - Testing Rationale

Four chemicals were placed into Group I because structurally they are all highly related. They all have a phenyl moiety containing two chlorine atoms in para- position to each other, and contain a carboxylate moiety on the phenyl ring. A summary of the data for this group is shown in Table 3 and a completed SIDS data matrix is provided in Section 4. An extensive battery of toxicology testing has been conducted on dicamba, many under Good Laboratory Practices (GLP); therefore, data for the SIDS toxicity endpoints for this group are covered mostly by data read across from dicamba. Additional mammalian toxicity studies and EPIWIN estimates for physicochemical data support data read across.

Physicochemical Properties

Measured data for melting point, vapor pressure, partition coefficient, and water solubility are available for dicamba. In addition, measured data are available for the melting point for dicamba, sodium salt. EPIWIN modeling for the remaining physicochemical endpoints for the chemicals in the group was conducted. It must also be remembered that some of these parameters are highly pH dependent when ionizable groups are included. For the needs of the HPV Program, estimation and read across provide sufficiently reliable information and no further physicochemical testing is recommended for Group I.

Environmental Fate

Environmental fate data for Group I was developed using both measured and EPIWIN model results for dicamba, and the other members of the group. Dicamba's $t_{1/2}$ for photodegradation in water was found to be 50 days. In a hydrolysis test (performed in amber bottles), it was found to be stable in water. Read across is appropriate for primary photodegradation in water for all other group members, but indirect photodegradation in air was also calculated for all members using EPIWIN. Based on the EQC Level III model, it is predicted that dicamba will be distributed to soil (80.2%) and water (19.6%) under conditions of equal emission to water, soil and air. In a ready biodegradability study conducted according to OECD Method 301F, biodegradation of dicamba was not observed under test conditions. Although dicamba is not readily biodegradable, there is other evidence that it can biodegrade under aerobic and anaerobic conditions.

Ecotoxicity

Acute fish, daphnia and algae inhibition studies were conducted for dicamba, with data available for both freshwater and saltwater species. Dicamba has a moderate acute ecotoxicity to fish with a 96-hr LC50 = 134.5 for rainbow trout (*Salmo gairdneri,* currently known as *Oncorhynchus mykiss*), 112 and 36.3 mg/L for bluegill sunfish (*Lepomis macrochirus)*, and > 180 mg/L for the estuarine species, sheepshead minnow (*Cyprinodon variegatus).* The 48-hr EC50 for the water flea (*Daphnia magna*) is 110.7 mg/L. For the freshwater green alga, *Selenastrum capricornutum*, the EC50 is > 3.7 mg/L. Based on the high degree of structural similarity between the chemicals in Group I, and the expected dissociation of the salts in the aquatic environment, testing for dicamba adequately covers the SIDS ecotoxicity endpoints for the other Group I chemicals and no further testing is warranted.

Mammalian Toxicity

A robust set of mammalian toxicity data was located for Group I chemicals, including several acute toxicity tests via the oral, dermal and inhalation routes of administration and a multigenerational reproduction/developmental test. Data are available for dicamba and dicamba, sodium salt and the results support the chemical categorization and data read across.

The data indicate the chemicals in Group I have a low acute toxicity via the oral, dermal and inhalation routes of exposure. Dicamba had the following acute toxicities: rat, oral LD50 = 1465 mg/kg; rabbit, dermal LD50 >1716 mg/kg; and rat, inhalation LC50 > 8200 mg/m^3. For dicamba, sodium salt the oral LD50 for the rat is > 1000 mg/kg and the dermal LD50 for the rabbit is > 400 mg/kg. The similarity in acute toxicity values between dicamba and dicamba, sodium salt further support the Group I categorization and the position that acid and salt forms will have equivalent toxicities.

The data also showed that dicamba is not expected to demonstrate genetic toxicity, as it was generally negative in both *in vitro* and *in vivo* genotoxicity studies. It was negative in an Ames assay in four strains (TA98, TA100, TA1535 and TA1537) with and without metabolic activation, and negative in an *in vitro* chromosomal aberration assay in Chinese hamster ovary (CHO) cells. Several *in vivo* studies for dicamba exist. Of the reliable studies, SCE frequency was increased in one study but not clearly positive in another SCE study, and dicamba was not clastogenic in the mammalian bone marrow chromosomal aberration test.

In a 13-week dietary study, male and female rats were exposed to 500, 3000, 6000, and 12000 ppm dicamba. At the highest dose, there was a lower rate of bodyweight gain in both sexes with a reduced food intake, associated neuro-behavioral signs, significant changes in hematology and clinical chemistry parameters, and increased liver weight. The NOAEL was 6000 ppm, equivalent to 479 mg/kg bw/day in males and 535 mg/kg bw/day for females.

In another 13-week dietary study, male and female rats were exposed to 1000, 5000 and 10000 ppm dicamba. Overall, the results showed a NOAEL = 5000 ppm based on effects on body weight, food consumption and elevated alkaline phosphatase (ALP) levels.

For developmental toxicity and toxicity to reproduction, a robust set of studies was available for dicamba, which included multigenerational studies in rats and teratogenicity studies in rats and rabbits. The results indicate the chemicals in Group I have a low developmental and reproductive toxicity, and are not teratogenic. In a 2-generation study, rats were exposed to dicamba at concentrations of 500, 1500 and 5000 ppm in the diet. Results indicated a parental and F1 NOAEL = 1500 ppm based on decreased female body weight gain during pregnancy and increased liver weights in both sexes and impaired growth of F1 offspring, and a developmental NOAEL = 500 ppm based on slightly reduced growth of F2-pups. No teratogenic effects were seen in either rats or rabbits during gestational day (GD) exposure studies. In one study, rats were exposed to dicamba via oral gavage on GD 6-19 at doses of 64, 160 and 400 mg/kg-bw. The maternal NOAEL = 160 mg/kg-bw based on decreased body weights, food consumption and clinical symptoms while the teratogenicity NOAEL = 400 mg/kg-bw based on the absence of any significantly increased malformations or variations. In the second study, pregnant rabbits were exposed by oral gavage to dicamba on GD 6-18, to doses of 30, 50 and 300 mg/kg-bw. Results indicated the maternal NOAEL = 30 mg/kg-bw based on loss of pregnancy and clinical signs, while the teratogenicity NOAEL = 300 mg/kg-bw based on the absence of any significantly increased malformations or variations.

Overall, the SIDS data set for mammalian toxicity data is robust and it is concluded that no further mammalian toxicity testing is warranted for Group I.

Table 3
Summary of Data Gap Analysis for Group I

SIDS Level I Endpoint	Dicamba (1918-00-9)	Dicamba, sodium salt (1982-69-0)	3,6-Dichloro-2-hydroxybenzoic acid, potassium sodium salt (68938-79-4)	3,6-Dichloro-2-hydroxybenzoic acid, dipotassium salt (68938-80-7)
Physicochemical Properties				
Melting point	A	A	A	A
Boiling point	A	NA[1]	NA[1]	NA[1]
Vapor pressure	A	A	A	A
Partition coefficient	A	A	A	A
Water solubility	A	A	A	A
Environmental Fate				
Photodegradation	A	R	R	R
Hydrolysis	A	A	A	A
Fugacity	A	A	A	A
Biodegradability	A	R	R	R
Ecotoxicity				
Acute fish	A	R	R	R
Acute daphnia	A	R	R	R
Algal inhibition	A	R	R	R
Mammalian Toxicity				
Acute mammalian	A	A	R	R
Gene Tox – Mutagenicity	A	R	R	R
Gene Tox – Clastogenicity	A	R	R	R
Repeat Dose	A	R	R	R
Repro or Development	A	R	R	R

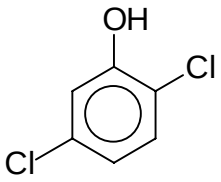
A = Adequate Data Exist (empirical or modeled), R = Read Across, T = Testing Proposed, NA = Not Applicable

[1]These compounds decompose rather than boil.

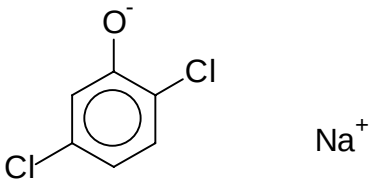
3.2 Group II

3.2.1 Chemistry

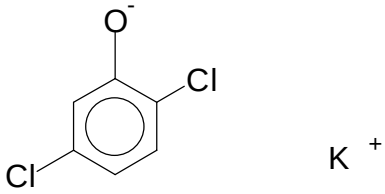
5. CAS 583-78-8: 2,5-Dichlorophenol



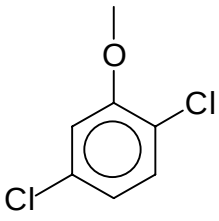
6. CAS 52166-72-0: 2,5-Dichlorophenol, sodium salt



7. CAS 68938-81-8: 2,5-Dichlorophenol, potassium salt



8. CAS 1984-58-3: 2,5-Dichloroanisole



The chemicals in Group II consist of 2,5-dichlorophenol, two of its salts and an intermediate. These chemicals are similar to those in Group I in that the central part of the structure all the Group II chemicals have a phenyl moiety containing two chlorine atoms in para- position to each other. Furthermore, all chemicals in Group II bear an oxygen atom that is directly attached to the phenyl ring. This oxygen atom is present either as part of a methoxyl group (chemical 8) or a functionalized (chemical 6 and 7) or free hydroxyl group (chemical 5).

The different functionalization of the oxygen atom as a methoxyl or hydroxyl group attached to the phenyl ring is not predicted to have a significant influence on the carbon ring reactivity of the chemical. Both hydroxyl and methoxyl substituents are strongly activating ortho- and para-directors (that is, activating the phenyl ring towards electrophilic aromatic substitution). They activate the phenyl ring by resonance donation of oxygen pi electrons, and for this it does not matter whether the oxygen is present as a free or functionalized hydroxyl group or as part of the methoxyl group. Hence, the chemicals in Group II are expected to have equivalent chemical reactivity regardless of whether they contain a methoxyl or hydroxyl moiety.

Although there are differences in the chemical reactivity of hydroxyl versus methoxyl groups, a common metabolite arises during biotransformation; therefore, similar toxicity is expected for all members of the group.

3.2.2 Toxicokinetics and Toxicodynamics

Group II chemicals consist of 2,5-dichloroanisole, 2,5-dichlorophenol and its sodium and potassium salt. All the chemicals in Group II are expected to have similar biotransformation pathways and elimination rates due to the high degree of structural similarity. The salt forms and the covalent forms are expected to have similar absorption from the gastrointestinal tract and other toxicokinetic processes, such as tissue distribution and systemic clearance (Caux et al., 1993, BASF,1994).

Studies have shown that the highest concentrations of dichlorophenols are found in liver, kidney and/or spleen, with peak levels occurring 15 minutes after administration (Sloff, et al.,1991, WHO, 1989). 2,5-Dichlorophenol and its salts will be subjected to direct conjugation of the hydroxyl-group with glucuronide or sulfate and will be eliminated quickly from the body via urine (Sloff, et al.,1991, WHO, 1989). 2,5-Dichloroanisole, however, contains a methoxyl-group and demethylation of the methoxyl group, or hydroxylation of the benzene ring, will occur prior to conjugation and concomitant elimination. No significant difference in overall toxicity is expected, although elimination from the body may be slower as compared to 2,5-dichlorophenol and its salts,

3.2.3 Group II - Testing Rationale

Four chemicals were placed into Group II because they are all highly related structurally. They all have a phenyl moiety containing two chlorine atoms in para- position to each other, and contain an oxygen atom that is directly attached to the phenyl ring as part of a methoxyl group or hydroxyl group.

A summary of the data for this group is shown in Table 4 and a completed SIDS data matrix is provided in Section 4. 2,5-Dichlorophenol has been extensively tested, including several studies under GLP; therefore, health-effects data for the SIDS endpoints for this group are covered mostly by data read across from this chemical. Additional mammalian toxicity studies and EPWIN estimates for physicochemical data support data read across. Where data gaps for the chemicals in this group previously existed (ecotoxicity endpoints), GLP studies on 2,5-dichlorophenol, sodium salt and on 2,5-dichloroanisole have been conducted.

Physicochemical Properties

Measured data on melting point, boiling point, and water solubility are available for 2,5-dichlorophenol, while the vapor pressure and partition coefficient were predicted with EPIWIN or other SAR. To evaluate the accuracy of the EPIWIN estimates, modeling was done for the parameters for which measured data was available and the modeled data was compared to the measured data. The measured data for 2,5-dichlorophenol are in good agreement with the EPIWIN predictions (the measured data and EPIWIN predictions for melting point and boiling point were 59°C and 47°C, and 211°C and 234°C, respectively).

For 2,5-dichlorophenol, sodium salt, a study was conducted according to OECD guideline 102 to determine the melting point (Lezotte and Nixon, 2005). The experimentally determined value of 350°C agrees precisely with the EPIWIN prediction via the Joback method. Using the experimentally-derived melting point as an input value, EPIWIN estimates for the remaining physicochemical properties were calculated. A melting point of 350°C was also used as an input value to calculate EPIWIN estimates for the physicochemical properties of 2,5-dichlorophenol, potassium salt.

Studies were conducted under GLP to determine the physicochemical properties of 2,5-dichloroanisole (BASF, 2004). The measured values for melting point, boiling point, vapor pressure, partition coefficient, and water solubility are all in good agreement with the predictions from EPIWIN modeling.

These results further support the Group II categorization as the values calculated for 2,5-dichloroanisole are in good agreement with those values for 2,5-dichlorophenol, both measured and EPIWIN predicted. Based on a review of the data, and the chemical categorization approach, sufficient data on SIDS endpoints for physicochemical parameters is available and no further testing is warranted for Group II.

Environmental Fate

Biodegradation data for 2,5-dichlorophenol were reported from the MITI-I test (equivalent to OECD 301 C) and from the literature. No biodegradation was observed during the 28 days of the MITI test, while 52% biodegradation in 4 days using adapted activated sludge was reported by Ingols (1966). A biodegradation study was conducted according to OECD Guideline 301 F with 2,5 dichloroanisole. The test substance was not degraded under the conditions of the test (less than 10% degradation in 28 days). All other environmental fate data for Group II was developed using the EPIWIN model. These results support read across for the chemical category and no further environmental fate testing is needed.

Ecotoxicity

Testing was conducted to fulfill the ecotoxicity endpoints for the Group II chemicals. Acute toxicity tests with rainbow trout, *Daphnia magna*, and green algae were performed under GLP for both 2,5-dichlorophenol, sodium salt and 2,5-dichloroanisole. Data were also available for two freshwater fish species for 2,5-dichlorophenol. The available data for fish indicates a high degree of agreement for 2,5-dichlorophenol, its sodium salt, and 2,5-dichloroanisole. The toxicity of 2,5-dichlorophenol, potassium salt is expected to be similar. The available data for invertebrates and algae show reasonably good agreement as well. Ecotoxicity endpoints are considered fulfilled and no further testing is needed.

Mammalian Toxicity

Data for mammalian toxicity are available for 2,5-dichlorophenol, demonstrating low acute toxicity via the oral, dermal and inhalation routes of exposure. 2,5-Dichlorophenol had the following acute toxicities: rat, oral LD50 = 2475 mg/kg; rabbit, dermal LD50 >8000 mg/kg and rat, inhalation LC50 >185000 mg/m^3.

Toxicity test data are available for 2,5-dichlorophenol that demonstrate it does not cause genetic toxicity. It was negative in an *in vitro* gene mutation test assay (OECD 476) using hypoxanthine-guanine phosphoribosyl transferease (HGPRT) loci as well as negative in the Ames assay, and was negative in an *in vivo* chromosomal aberration study in mice.

There are sufficient studies that evaluate the sub-chronic toxicity of the chemicals in this Group because two repeated dose studies are available for 2,5-dichlorophenol and repeated dose toxicity was evaluated in an OECD 422 study with 2,5-dichloroanisole. In a 21-day test, male and female rabbits were exposed dermally to 2,5-dichlorophenol 5 days/week, 6 hours/day to 1, 10 and 100 mg/kg-bw. The results indicate a NOAEL = 100 mg/kg-bw based on systemic effects. In a 28-day inhalation test, male and female rats were exposed to 2,5-dichlorophenol 5 days/week, 6 hours/day at concentrations of 100, 300 and 1000 mg/m3. In this study a LOAEL = 100 mg/m^3 (0.1 mg/L) was reported based on liver effects. A combined repeated dose with reproductive/developmental toxicity screening test (OECD 422) was conducted for 2,5-dichloroanisole (Schneider et al., 2006). The parental rats were exposed by gavage for a total period

of 35 days (males) or 44 days (females) to 50, 150 and 450 mg/kg bw/day. The NOAEL was identified as 150 mg/kg bw/day based upon impairments of food consumption and body weight data for the high dose females and a higher incidence and severity of chronic progressive nephropathy in high dose males. These three studies, which cover male and females in two different species and three different routes of administration, for two of the four chemicals in the category, adequately address the repeat dose toxicity testing SIDS endpoints for the group.

To address toxicity to reproduction and development, a combined repeated dose with reproduction /developmental toxicity screening test was conducted for 2,5-dichloroanisole (Schneider et al., 2006). Rats were dosed by gavage at 50, 150 and 450 mg/kg bw/day. At least 13 days after the beginning of treatment, males and females from the same dose group were mated. Exposure of the parental animals then continued, totaling 35 days (males) or 44 days (females, encompassing gestation, parturition and lactation for 4 days after parturition). No effects were observed in reproductive parameters for either sex. The NOAEL for reproductive performance and fertility was the highest dose tested, 450 mg/kg bw/day. No test substance related signs occurred in the progeny, so the NOAEL for teratogenicity was also the highest dose, 450 mg/kg bw/day.

The mammalian toxicity data for 2,5-dichlorophenol and 2,5-dichloroanisole are adequate to fulfill the mammalian toxicity SIDS endpoints for the chemicals in Group II and no additional testing is needed.

Table 4
Summary of Data Gap Analysis for Group II

SIDS Level I Endpoint	2,5-Dichlorophenol (583-78-8)	2,5-Dichlorophenol, sodium salt (52166-72-0)	2,5-Dichlorophenol, potassium salt (68938-81-8)	2,5-Dichloroanisole (1984-58-3)
Physicochemical Properties				
Melting point	A	A	A	A
Boiling point	A	NA[1]	NA[1]	A
Vapor pressure	A	A	A	A
Partition coefficient	A	A	A	A
Water solubility	A	A	A	A
Environmental Fate				
Photodegradation	A	A	A	A
Hydrolysis	A	A	A	A
Fugacity	A	A	A	A
Biodegradability	A	A	A	A
Ecotoxicity				
Acute fish	R	A	R	A
Acute daphnia	R	A	R	A
Algal inhibition	R	A	R	A
Mammalian Toxicity				
Acute mammalian	A	R	R	R
Gene Tox – Mutagenicity	A	R	R	R
Gene Tox – Clastogenicity	A	R	R	R
Repeat Dose	A	R	R	A
Repro or Development	R	R	R	A

A = Adequate Data Exist (empirical or modeled), R = Read Across, T = Testing Proposed, NA =Not Applicable

[1]These compounds decompose rather than boil.

3.3 Test Plan Summary

All testing proposed in the previous test plan and recommended by U.S. EPA in review of the previous test plan has been completed. For Group I, this includes a biodegradation study with dicamba and a melting point study with dicamba, sodium salt. For Group II, this includes the following studies with 2,5-dichloroanisole: boiling point, vapor pressure, partition coefficient, water solubility, biodegradation, acute fish, acute daphnia, algal inhibition, and combined repeated dose/reproduction study. Also for Group II, the following studies were completed with 2,5-dichlorophenol, sodium salt: melting point, acute fish, acute daphnia, and algal inhibition.

4.0 SIDS Data Matrix

4.1 SIDS Matrix – Group I

SIDS Endpoint	Dicamba (1918-00-9)		Dicamba, sodium salt (1982-69-0)		3,6-Dichloro-2-hydroxybenzoic acid, potassium sodium salt (68938-79-4)		3,6-Dichloro-2-hydroxybenzoic acid, dipotassium salt (68938-80-7)	
Physicochemical	**Value**	**Comment**	**Value**	**Comment**	**Value**	**Comment**	**Value**	**Comment**
Melting point (°C)	87-108	Sandoz, 1993a	320 -325	Widlak, 1994	220	EPIWIN	220	EPIWIN
Boiling point (°C)	329	EPIWIN						
Vapor pressure (hPa)	1.67e-05	Sandoz, 1994a	Nil	EPIWIN	Nil	EPIWIN	Nil	EPIWIN
Partition coefficient	2.21	Hansch et al., 1995	-0.90	EPIWIN	-4.15	EPIWIN	-4.15	EPIWIN
Water Solubility (g/L)	8.24	Sandoz, 1993b	2.6	EPIWIN	1000	EPIWIN	1000	EPIWIN
Environmental fate								
Photodegradation (t1/2, days)	50.3(in water); 3.6 (in air)	Sandoz, 1993c; EPIWIN	50.3 (in water); 2.2 (in air)	Sandoz, 1993c; EPIWIN	2.7	EPIWIN	2.6	EPIWIN
Hydrolysis	Stable	Velsicol, 1981	Stable	Velsicol, 1981	Stable		Stable	
Fugacity	19.6% Soil 80.2% Water	EQCIII	48.1% Soil 51.2% Water	EQCIII	50.4% Soil 49.5% Water	EQC III	50.4% Soil 49.5% Water	EQC III
Biodegradability	Not readily biodegradable	Wallace and Daniel, 2001						
Ecotoxicity								
Acute Fish – LC50 (mg/L)	134.5 (*S. gairdneri)*	Velsicol, 1997a						
Acute Daphnia – EC50 (mg/L)	110.7 (*D. magna)*	Velsicol, 1997b						
Algal Inhibition – EC50 (mg/L)	>3.7(*S. capricornutum)*	Sandoz, 1993d						
Mammalian								
Acute – Oral (mg/kg)	1465 (rat)	Velsicol, 1974	>1000 (rat)	Velsicol, 1982a				
Acute – Dermal (mg/kg)	>1716 (rabbit)	Velsicol, 1974	>400(rabbit)	Velsicol, 1982b				
Acute – Inhalation (mg/m^3)	>8200 (rat)	Velsicol, 1974						
Gene Tox – Mutagenic	Negative (Ames Assay)	Ballantyne, undated						
Gene Tox – In-vitro Cytogenetic	Negative (chromosomal aberration)	Microbiological Associates, 1986						
Gene Tox – In-vivo Cytogenetic	Negative and positive results in SCE test; negative in bone marrow test	Gonzales et al. 2006; Perocco et al., 1990; Hrelia et al., 1994.						
Repeat Dose – 13-Week Rat, Oral NOAEL (mg/kg-bw)	479 (males); 535 (females)	Novartis, 1997						

SIDS Endpoint	Dicamba (1918-00-9)		Dicamba, sodium salt (1982-69-0)		3,6-Dichloro-2-hydroxybenzoic acid, potassium sodium salt (68938-79-4)		3,6-Dichloro-2-hydroxybenzoic acid, dipotassium salt (68938-80-7)	
Reproduction – 2-Gen Rat, Oral, NOAEL (ppm)	1500 (Parental and F1); 500 (F2)	Huntingdon Research Centre, 1993						
Developmental – Rat, Oral NOAEL(mg/kg-bw)	160 (maternal tox); 400 (terato-genicity and fetotoxicity)	ToxiGenics, 1992						
Developmental – Rabbit, Oral NOAEL(mg/kg-bw)	30 (maternal tox); 300 (terato-genicity and fetotoxicity)	Argus Research Labs, 1992						

4.2 SIDS Matrix – Group II

SIDS Endpoint	2,5-Dichlorophenol (583-78-8)		2,5-Dichlorophenol, sodium salt (52166-72-0)		2,5-Dichlorophenol, potassium salt (68938-81-8)		2,5-Dichloroanisole (1984-58-3)	
Physicochemical	**Value[1]**	**Comment**	**Value**	**Comment**	**Value**	**Comment**	**Value[1]**	**Comment**
Melting point (°C)	59 (47)	Handbook; (EPIWIN)	350	Lezotte and Nixon, 2005	350	EPIWIN	19.9 (20.7)	BASF, 2004
Boiling point (°C)	211 (234)	Handbook; EPIWIN					231.3 (215.7)	BASF, 2004
Vapor pressure (hPa)	0.08	EPIWIN	Nil	EPIWIN	Nil	EPIWIN	0.07 (0.22)	BASF, 2004
Partition coefficient	3.06 (3.20)	Hansch et al., 1995; EPIWIN	0.12	EPIWIN	0.12	EPIWIN	3.5 (3.36)	BASF, 2004
Water Solubility (mg/L)	2000 (614)	Borzelleca et al,. 1985; EPWIN	190	EPIWIN	184	EPIWIN	84-90 (76)	BASF, 2004
Environmental fate								
Photodegradation (t1/2 days)	1.5	EPIWIN	2.42	EPIWIN	2.42	EPIWIN	2.0	EPIWIN
Hydrolysis	Stable		Stable		Stable		Stable	
Fugacity	80.9% Soil 17.8% Water	EQCIII	50.8% Soil 48.2% Water	EQCIII	54.3% Soil 45.6% Water	EQCIII	74.9% Soil 17.8% Water	EQCIII
Biodegradability	Not readily biodegradable but reported to biodegrade somewhat	NITE, 2007; Ingols, 1986	Primary biodegradation: days to weeks	EPIWIN	Primary biodegradation in weeks	EPIWIN	Poorly biodegrade-able	Schwarz, 2004
Ecotoxicity								
Acute Fish – LC50 (mg/L)	3.3 (*P. flesus* and *O. latipes*)	As cited in ECOTOX, 2007	3.2 (*O. mykiss*)	Palmer et al., 2005a			2.4 (*O. mykiss*)	Zok, 2005
Acute Daphnia – EC50 (mg/L)			15 (*D. magna*)	Palmer et al., 2005b			5.89 (*D. magna*)	Jatzek, 2005
Algal Inhibition – EC50 (mg/L)			0.34 (*S. capricornutum*)	Desjardins et al., 2005			8.1 (*S. subspicatus*)	Werner, 2005
Mammalian								
Acute – Oral (mg/kg)	2475 (rat)	Hoechst, 1976						
Acute – Dermal (mg/kg)	>8000 (rabbit)	IRDC, 1974						
Acute – Inhalation (mg/m^3)	>185000 (rat)	IRDC, 1974						

SIDS Endpoint	2,5-Dichlorophenol (583-78-8)		2,5-Dichlorophenol, sodium salt (52166-72-0)		2,5-Dichlorophenol, potassium salt (68938-81-8)		2,5-Dichloroanisole (1984-58-3)	
Gene Tox – Mutagenic	Negative (HGPRT assay and Ames Assay)	Bayer, 2000; Tegethoff, 2000; Haworth et al., 1983.						
Gene Tox – *In vivo* Cytogenetic	Negative (micronucleus)	Bayer, 2000; Tegethoff, 2000						
Repeat Dose – 34-43 days, Rat, oral, NOAEL (mg/kg bw)							150	Schneider et al., 2006
Repeat Dose – 28-day Rat, Inhalation LOAEL (mg/L)	0.1 (rat)	IRDC, 1980a						
Repeat Dose – 21-day Rabbit, Dermal NOAEL (mg/kg-bw)	100 (rabbit)	IRDC, 1980b						
Reproduction – NOAEL (mg/kg-bw)							450 (parental and F1)	Schneider et al., 2006
Developmental – NOAEL(mg/kg-bw)							150 (maternal); 450 (terato-genicity)	Schneider et al., 2006

[1] EPIWIN predicted value given in parentheses

5.0 References

This list of references is for studies as cited in Sections 1-4, while a complete list of all data sources reviewed in the development of Robust Summaries and Test Plan for Dicamba Intermediates Category is provided in the Robust Summaries.

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